



Attorney's Docket No. 7753-113

Patent

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of)
)
Jean-Pierre Robin, et al.) Group Art Unit 1624
)
Application No. 09/270,006) Examiner: Venkataraman Balasubramanian
)
Filed: March 16, 1999) Confirmation No.: 1899
)
For: Novel Cephalotaxane Derivatives and)
Process for Their Preparation)

DECLARATION UNDER 37 C.F.R. § 1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Jean-Pierre Robin, hereby declare that:

1. In 1967 I was a graduate in Clinical Biology. In 1970 I was a graduate in Physical Chemistry and Organic Chemistry and received a license in Sciences at Le Mans. In 1970 I was a fellow in Clinical Biochemistry, Hematology, Microbiology, and Parasitology. In 1971 I was a graduate in Macromolecular Chemistry at Le Mans. In 1972 I was a Pharmacist at Tours. In 1975 I was a graduate in Immunology at Nantes. In 1979 I was a doctorate in Sciences, Ph.D., at Le Mans.

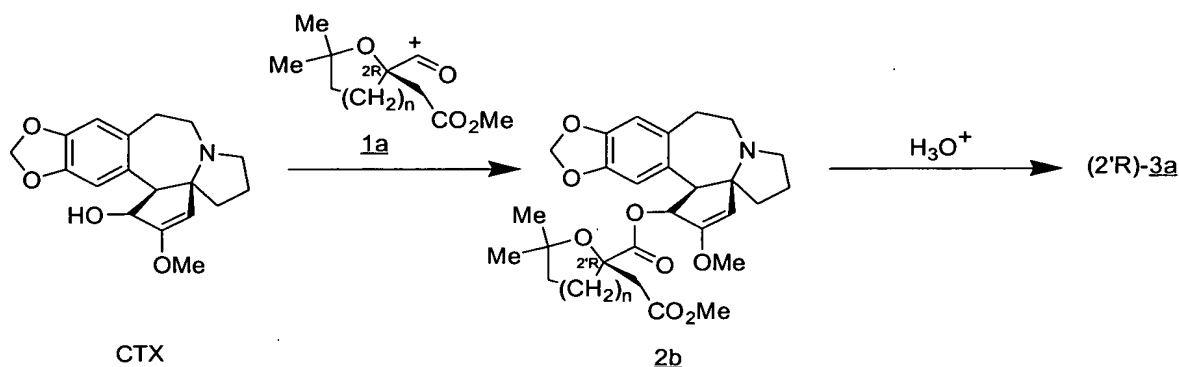
2. I am president, CEO, and major shareholder of Oncopharm Corporation.

3. Attached as Appendix A is my resume.

4. I am familiar with and a named inventor on the above-referenced patent application.

5. As exemplified by scheme 1,

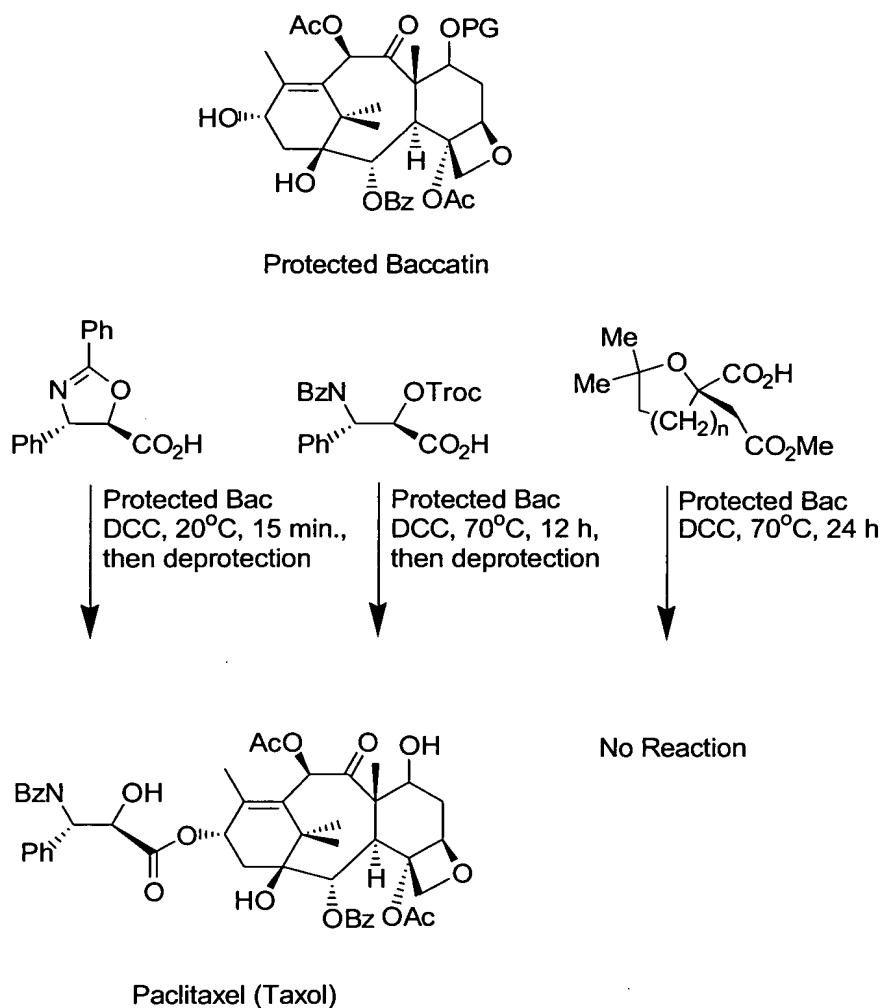
Scheme 1



the present invention consists of the direct esterification of a pentacyclic alkaloid such as cephalotaxine (CTX) by a bulky side-chain precursor such as 1a, in which the backbone and stereochemistry are preformed. Because of the very high steric hindrance of both the side-chain and the alkaloid moieties, the formation of esters such as (2'R)-3a was unexpected, if not impossible, see for example the Hudlicky literature review. Hudlicky, T., et al., *Synthesis of Cephalotaxine Alkaloids*, The Alkaloids, Vol. 51, Chapter 5, 1998, pp. 639-691, Academic Press, Burlington, MA., USA.

6. According to personal experience in paclitaxel semi-synthesis (see scheme 2 below and attached resume), esterification of a hindered alcohol such as protected Baccatin, with a bulky linear side-chain is difficult, and a large contact time and high temperature are necessary.

Scheme 2

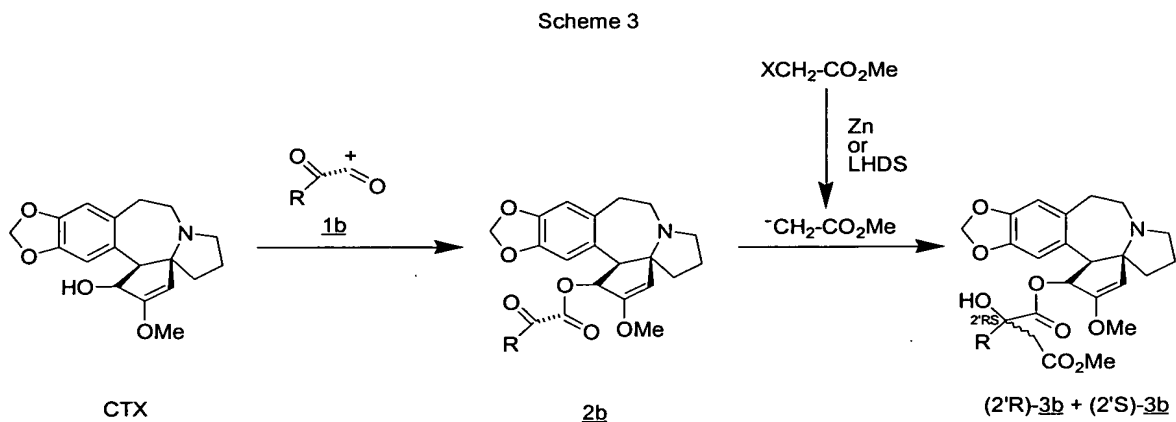


When hindrance is reduced such as in a side-chain in cyclic form, the coupling of the two moieties is greatly facilitated (see scheme 2). However, when the hydroxyl in the alpha position of the carbonyl is free or protected by an excessively bulky protective group, the esterification becomes difficult or impossible even at high temperature.

7. In addition, we experienced that the esterification of protected Baccatin (the precursor of paclitaxel semi-synthesis) by 1a ($n = 2$) failed consistently, whereas a similar cyclic side-chain without a branching in the alpha position easily gave the wanted ester as direct precursor of paclitaxel (Taxol) (see scheme 2 and attached resume). Because the hydroxyl of cephalotaxine is

considered very hindered, the success of the esterification of cephalotaxine by 1a was even further unexpected, a crucial point which shows the inventive aspect of this step.

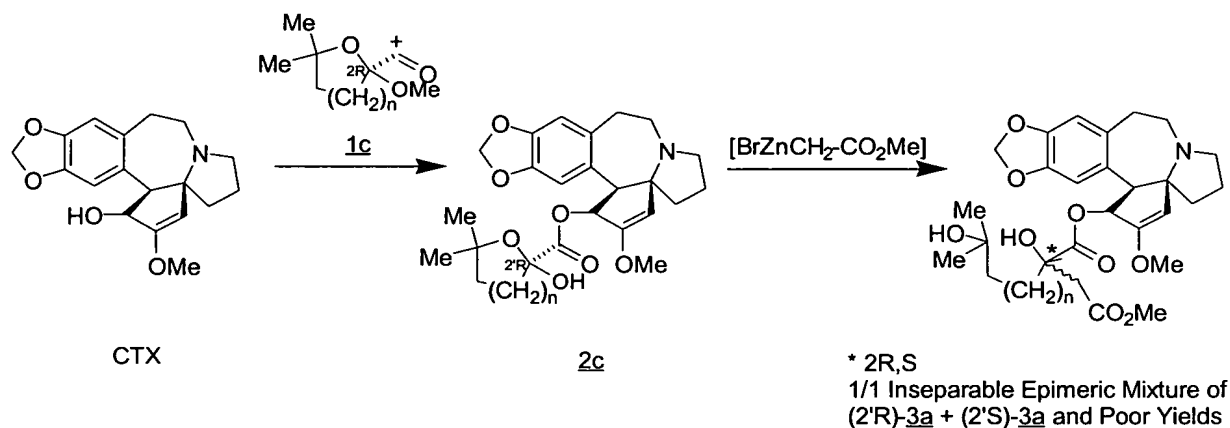
8. As summarized in scheme 3,



and in the Hudlicky recent review, every synthesis described in the literature used an alpha keto-acid (or its acylating form) such as 1b in which R cannot have a free hydroxyl, for the esterification of the hydroxyl of cephalotaxine, to give the alpha-keto ester 2b. Then this keto-ester is submitted to alpha-hydroxylation by the anion of ethyl acetate, generated mostly by a Reformatsky reaction, to give a 1/1 inseparable epimeric mixture of (2'R+2'S)-3b, in poor yield. In summary, the anchorage of the -CH₂CO₂Me secondary side-chain after esterification is not able to give a product suitable for pharmaceutical use (but only an inseparable epimeric mixture) and in acceptable environmental conditions related to biodiversity conservation (because Cephalotaxus is a rare and endangered tree and the reaction has a low yield).

10. The Wang II synthesis cited by the examiner, scheme 4,

Scheme 4



circumvents the difficulty of the presence of the free alcohol by including it in a mixed cyclic acetal but does not overcome the inconvenience of the non-stereoselectivity of the post-esterification alpha-hydroxyalkylation, the low yield of the reaction, or the purification of the final epimeric mixture.

11. The description of (2'R)-3a (for $n = 1$: anhydro-harringtonine; for $n = 2$: anhydro-homoharringtonine) in Wang I, the existence of this intermediate in nature, and finally its retrosynthesis by cyclisation of 2a (the final product of our synthetic scheme) demonstrate that 3a synthesis (in fact retro-synthesis) is chemically possible by a method other than direct esterification from cephalotaxine, but do not provide any argument to predict that either ring opening or direct esterification of cephalotaxine by a hindered side-precursor such as 2a are possible.

12. The sequence as described in Wang II is particularly well commented on in the Hudlicky review. Regarding compound 104, the review mentions page 662: "The exposure of this material to the organozinc reagent derived from methyl bromoacetate and active zinc gave under the conditions of the Reformatsky reaction a mixture of harringtonine and its epimer in a ration of 1:1,1. ... Both groups reported diminished yields of the Reformatsky reaction, because cleavage of the ester under the reaction conditions gave back cephalotaxine. The yields of harringtonine were reported to be 20 and 10%, respectively."

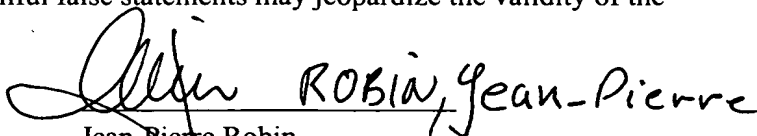
13. Regarding the esterification of cephalotaxine, the Hudlicky review states at page

661: "Most of the synthetic approaches to cephalotaxine esters are concerned [...]. **This is hardly surprising in view of the antitumor activities of these alkaloids. Attempts to prepare these esters by direct esterification of a particular side-chain derivative of cephalotaxine have been uniformly unsuccessful.**"

14. At page 679 of the same review, the author concludes the section related to cephalotaxine ester synthesis by stating: "The message left after nearly 15 years of intensive research in this field has informed synthetic chemists that the problem of esterification of cephalotaxine, the question of steric requirements of side-chain attachment and the overall efficiency of the syntheses were all grossly misjudged at the onsets of their investigations. These problems were not simple and are but partially solved today only because scores of investigators devoted their time to examining every possible detail of a deceptively elementary reaction in organic synthesis, namely, an esterification. ... Of special significance will be the design of syntheses with complete stereocontrol because the separation of isomers, especially the isomers differing in the stereochemistry of side-chain esters, proved extremely tedious and difficult."

15. If the Wang intermediate 3c described in 1978 would allow chemists to predict that harringtonines could be synthesized via intermediates such as 1a and to solve the problem of stereoselective synthesis of harringtonines, it is incomprehensible that these ideas did not appear in the chemist community for several decades. For this reason, we contend that no preceding work indicates that direct esterification of cephalotaxine by an ester bearing a hindered hydrocarbonated branched chain with a preformed asymmetric center in alpha of the carbonyl function was possible and that most of the inconvenience in the existing state of the art, as summarized in recent reviews, was overcome by the present invention.

16. I hereby declare that all statements made herein of our own knowledge are true and that all statements made upon information and belief are believed to be true; and further that these statements and the like so made are punishable by fine or imprisonment, or both, under 18 United States Code section 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.


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Date: August 16, 2002

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1967	Graduate in Clinical Biology	
1970	Graduate in Physical Chemistry	Le Mans
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	Licence in Sciences	Le Mans
1970	Fellow in Clinical Biochemistry, Hematology, Microbiology and Parasitology	
1971	Graduate in Macromolecular Chemistry	Le Mans
1972	Pharmacist	Tours
1975	Graduate in Immunology	Nantes
1979	Doctorat in Sciences, Ph.D.	Le Mans

Member of Academic Societies:

1970	Société Astronomique de France
1982	American Society of Pharmacognosy
1984	American Chemical Society
1996	American Association of Pharmaceutical Scientists
1998	Société Chimique de France
2000	Parenteral Drug Association

From 1972 to now: Successively manager and president of 11 companies and non-profit organizations:

1973 :Drouard Clinical Laboratory: Manager
 1976 :Lardy and Robin Clinical Biology Laboratory: Manager and Owner
 1978: Medical Center Clinical Laboratory: Manager
 1980: Association for the Advancement of Anticancer Chemotherapy: President (non profit organisation)
 1987: Holdipharm (corporation): President and CEO and major shareholder.
 1987: Seripharm (corporation): President and CEO and major shareholder.
 1987: Taxopharm (corporation): President and CEO and major shareholder.
 1987: Phobos: President and major partner.
 1996: Paclipharm (corporation): President and CEO and major shareholder.
 1996: Oncopharm France (corporation) : President and CEO and major shareholder.
 1996: Paclipharm France and major shareholder.
 1998: Oncopharm Corporation: President and CEO and major shareholder.

Know-now in production of chemotherapeutic agents

Production of podophyllotoxin, etoposide and teniposide
 Production of vincristine
 Production of daunosamine and doxorubicine
 Production of cis-platin
 Production of 10-deacetylbaccatin III, paclitaxel (Taxol), docétaxel (Taxotere)
 Production of cephalotaxine and homoharringtonine

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International Journal of Oncology
Journal of Hypertension
Journal of Clinical Immunology
Pharmacological Research Communications
Prostaglandins

Applied Organic Chemistry (total synthesis of natural compound)

Compte-Rendu de l'Académie des Sciences (Paris)
Journal of The Chemical Society, Chemical Communications
Journal of Natural Products
Journal of Organic Chemistry
Tetrahedron
Tetrahedron Letters

Fundamental Organic CHEMistry (catalysis, reaction, synthesis)

Journal of The Chemical Society, Chemical Communications
Journal of Organic Chemistry
Tetrahedron
Tetrahedron Letters

Structural Chemistry (Conformational Studies : RX, NMR...)

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Tetrahedron
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Pharmacognosy, Phytochemistry

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Vol 3, p 501, 502, 509, 512, 513

Lignans (Ayres and Loykes

20 citations.